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EXAMINER	
PORTNER, VIRGINIA ALLEN	

ART UNIT	PAPER NUMBER
1645	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/893,615	Applicant(s) Fischer et al
	Examiner Portner	Art Unit 1645

-- Th MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 14, 2003*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *32-44* is/are pending in the application.

4a) Of the above, claim(s) *41* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *32-40 and 42-44* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *32-44* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *17*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 32-44 are pending.

Claims 1-31 have been canceled.

Claims 32 and 37 have been amended.

Claims 32-40, 42-44 are under consideration.

Claim 41 stands withdrawn from consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

KSP 9/10/03

2. The information disclosure statement filed July 14, 2003 has been considered as to the merits prior to this action.

Rejections Withdrawn

3. Claims 32, 37 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the amendment of these claims to clarify the first occupance of the term "thereof" to refer to the recited antibody.

4. Claims 32-33 rejected under 35 U.S.C. 102(e) as being anticipated by Gristina et al (US Pat. 5,505,945), in light of the reconsideration of the disclosure of Gristina et al .

5. Claims 32-33 rejected under 35 U.S.C. 102(b) as being anticipated by Fattom et al (WO93/09811),in light of the reconsideration of the disclosure of Fattom et al (see pg 8, lines 9-15).

Objections/Rejections Maintained

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures; Figures 5, 7A & 7B show a plurality of sequences that are only identified by 4 and 6 SEQ ID Nos respectively. Amendment of the Brief Description of the Drawings to identify the recited sequences would place the Application into sequence compliance. The objection is being maintained as the sequences shown have not been described; all sequences must evidence a sequence identifier. Insertion of a statement in the Brief Description that recites the designators shown in the drawings together with a single SEQ ID NO could meet this requirement.

7. The Brief Description of the drawings objected to because the description of Figures 6A, 6B, 7A, 7B, 11A, 11B, 12A and 12B have not been described in the section of the specification. This objection is being maintained because, while an amendment of the specification was submitted directing the entry of the amendment on a specific page, no line numbers for the amendment were provided and the exact location for insertion of the amendment was not provided. Resubmission of an amendment that provides a page and line number for insertion of the amendment into the specification could obviate this objection.

8. Claim 32 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,955,074. Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed claims are directed to a species of method of treating Staphylococcus epidermidis infection, the immunoglobulin being selected against S.epidermidis teichoic acid antigen (see col. 6, lines 40-54) and the instantly claimed invention is directed to methods of treating any gram positive infection. A species anticipates the instantly claim genus.

9. Claim 32 rejected under 35 U.S.C. 102(b) as being anticipated by Dale et al (1994, abstract), for reasons of record in paper number 14, paragraph 15.

10. Claim 32 rejected under 35 U.S.C. 102(b) as being anticipated by Fischer (WO93/19373), for reasons of record in paper number 14, paragraph 16.

11. Claims 32-33 rejected under 35 U.S.C. 102(e) as being anticipated by Fattom et al (US Pat. 5,770,208)for reasons of record in paper number 14, paragraph 17.

12. Claim 32 rejected under 35 U.S.C. 102(b) as being anticipated by Ichiman et al (1989)for reasons of record in paper number 14, paragraph 20.

Response to Arguments

13. Applicant's arguments filed July 14, 2003 have been fully considered but they are not persuasive, because they are not commensurate in scope with the instantly claimed invention

14. The rejection of claim 32 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,955,074, is traversed on the grounds that:

a. the immunoglobulin of independent claim 1 of '074 is obtained from serum, plasma and an immunoglobulin pool and the TCA extract used to select Ig with specific binding to

S.epidermidis "contains several hundred antigens" and the Ig targets a broad spectrum of S.epidermidis antigens, whether a whole cell or TCA extract, rather than a species, this claim can be more accurately viewed as a genus.

15. It is the position of the examiner that the claimed invention of '074 administers directed human immune globulin. The directed human immune globulin is defined in the specification of '074 by a process which includes immunization of a host (see col. 8, lines 45-54) with a TCA extracted antigen of S.epidermidis, wherein the administered antigen composition which comprises LTA (see Naumova et al, 1980, reference cited in Applicants US-PTO 1449, dated October 7, 2002, page 6 of 9, method of obtaining TCA antigen of S.epidermidis of '074) for the induction of anti-teichoic acid S.epi antibodies.

Immune globulin produced through immunization with a TCA extracted S.epidermidis antigen which comprises LTA antigens (see Naumova et al, 1980, reference cited in Applicants US-PTO 1449, dated October 7, 2002, page 6 of 9, method of obtaining TCA antigen of S.epidermidis of '074, produces LTA containing antigen composition) would induce and produce a composition of anti-S.epidermidis teichoic acid (LTA) antibodies. Immune globulin administered produced through immunization with a composition that comprises teichoic acid, would result in a pharmaceutical composition that comprises anti-LTA antibodies of S.epi. All of the claims recite open language and therefore permit the presence of additional antibodies that bind to other antigens.

Comparison of Obvious Double Patenting References

Instant Claim 32(larger genus than '074)	'074 (species of instant genus claim 32)
method of treating **or** preventing (genus)	method of treating **and** preventing (species)
administering a pharmaceutical composition	administering directed human Ig (species)
composition comprising antibodies (genus)	composition of immune globulin (species)
antibodies to gram positive bacteria(genus)	antibodies for S.epidermidis (sp.of gram +)
antibodies are anti-LTA (genus)	antibodies (inherent)anti-S.epi LTA(species)
pharmaceutical carrier (genus)	Serum or plasma or Ig pool carrier (species)
> or = 75% opsonic activity(genus)	> or = 80% opsonic activity (species)

The Obviousness Type Double Patenting Rejection is maintained, as the administered composition has not been distinguished from that administered by '074.

16. The rejection of claims 32-40, 42-44 under 35 U.S.C. 112, first paragraph (scope of enablement), because the specification, while being enabling for the treatment and prevention of infection caused by Gram positive bacteria with a polyclonal antibody to Gram positive lipoteichoic acid obtained from Staphylococcus, or with a monoclonal antibody MAB96-110, does not reasonably provide enablement for the utilization of any monoclonal, fragment, region or derivative of an antibody that binds to any portion of a lipoteichoic acid, SEQ ID No 1 or 2, or is a derivative of SEQ ID NO 88 or 89, for the treatment or prevention of Gram positive bacterial infection, is traversed on the grounds that:

a. Claims 34,35,39,40 and 44 recite Mab 96-110 and therefore should not be rejected under the scope of enablement.

17. It is the position of the examiner that while claims 34,35, 39,40 and 44 recite Mab 96-110, the combination of claims limitations of claim 32 , with claims 34 and 35, does not limit the claimed methods of claims 34 and 35 to the utilization of the whole monoclonal antibody Mab 96-110 in the claimed method. The Fc fragment, any single region, or derivative of the Fc

fragment or derivative of any single region of Mab 96-110 have not been enabled for therapeutic or prophylactic treatment of gram positive infection. The allowed claims of US Pat. 6,610,293 comprise a human immunoglobulin that comprises a constant region and a variable non-human region which together have specificity for lipoteichoic acid of Gram positive bacteria. The allowed combination of regions and derivatives are not recited in claims 34 and 35. Claims 34 and 35 are not limited to just to Mab 96-110. Applicant arguments are not commensurate in scope with the instantly claimed combination of claim limitations recited in claims 34 and 35. Amendment of claims 34 and 35 to be commensurate in scope with Applicant's arguments could obviate this rejection for claims 34 and 35.

With respect to claims 39,40 and 44 which also recite Mab 96-110, the same arguments set forth for claims 34-35 immediately above apply to claims 39,40 and 44 . Amendment of claims 39, 40 and 44 to recite the Deposited monoclonal antibody alone as argued by Applicant could obviate this rejection for claims 39,40 and 44.

18. Applicant asserts that the disclosure of Fiedel et al (1972, abstract title) "does not stand for the proposition that antibodies to teichoic acid, a different antigen from LTA, cause kidney disease".

19. It is the position of the examiner that the claimed method may administer antibodies directed against any portion or fragment of lipoteichoic acid. Lipoteichoic acid is made up of a lipid component and a teichoic acid component. Teichoic acids comprise either a polyol of a ribitol phosphate or glycerol phosphate which carry dl-alanyl residues esterified to OH groups and glycosidically linked sugars. Therefore, the antibodies administered to a patient can be a composition of "anti-teichoic" acid antibodies, wherein Fiedel et al found anti-teichoic acid antibodies to induce kidney disease in rabbits.

If there is a specific epitope that is critical to the instantly claimed invention that binds to LTA that does not induce kidney disease, the claims are not so limited to the administration of

such an antibody as the claims administer antibodies of any binding specificity as long as the antibody(either polyclonal or monoclonal or chimeric or humanized) binds to any portion or epitope of LTA.

The antibodies of Fiedel which are anti-teichoic acid antibodies are within the scope of the instantly claimed invention. The rejection made of record is a scope of enablement, not a total lack of enablement of the instant invention. Amendment of the claims to recite the critical elements of the invention which provide protection, and exclude those antibody composition directed to teichoic acids that induce kidney disease could partially obviate this rejection.

20. With respect to Aasjord, P et al (1985, abstract), Applicant points to the fact that both MS patients and non-MS patients samples contained antibodies to LTA and therefore the antibodies to LTA did not cause MS pathogenesis.

21. It is the position of the examiner that Aasjord differentiates between the different antibody binding specificities present in MS patients and non-MS patients. At page 248, Table 1, the cerebral spinal fluid of MS patients (6 of 7 patients) were found to immunoreact with an epitope existing between alanine and glycerol-phosphate backbone of LTA (see page 249, col. 1, last two sentences of paragraph), while only 1 of 7 normal patients evidenced antibodies with this binding specificity. Aasjord et al concludes that the binding specificity of the human antibodies in MS patients differs from that of the antibodies in the non-MS group (see page 250, col. 1, sentence starting with the phrase "Taken together our data indicate"). Therefore the antibodies in the MS patients and the non-MS subjects are set forth as evidencing different binding specificity to LTA. As the binding specificity of the instantly claimed invention includes all antibodies that bind to LTA, the claims include the administration of antibodies that would be associated with MS; at no time did the examiner state that the antibodies cause MS pathogenesis. The route of administration does not exclude a mode that would result in effecting the CSF of a patient.

Clearly Aasjord et al (1985) provide evidence that all anti-LTA antibodies would not

serve to provide a therapeutic effect to treat gram positive bacterial infection upon administration to a patient, especially if they specifically bound to a subfragment of cardiolipin (see Aasjord et al, page 247, Results section, col. 1, paragraph 3) rather than binding to a gram positive bacteria's LTA to treat infection. Additionally Aasjord et al, provides evidence that anti-LTA antibodies are found in with MS patient cerebral spinal with a binding specificity that differs from that of antibodies found in biological samples from normal patients.

Given the clear, yet broad scope of the instantly claimed invention being directed to the administration of any anti-LTA antibodies, the full scope of the claimed invention is not enabled for the prevention or therapeutic treatment of gram positive infection through the administration of anti-lipoteichoic acid associated with multiple sclerosis patients or that would preferentially bind to cardiolipin rather than a gram positive bacterial pathogen in a method of treating gram positive bacterial infection.

All antibodies that bind to lipoteichoic acid epitopes would not provide means to prevent or treat any disease associated with a gram positive bacteria, because some antibodies are associated with pathological processes that are not preventative or therapeutic of gram positive bacterial infection, but could cause undesirable physiological effects (see Aasjord et al, page 247, col. 1, Results, paragraph 3).

22. With respect to Stashenko, P et al (1986, abstract), Applicant points to the fact that the enhanced adherence of gram positive pathogens was dose-dependent and points to the fact that bacterial adhesion may be an artifact of the way the adhesion assay was performed.
23. It is the position of the examiner that the assay provided insight into the importance of dosage size relative to the biological effects associated with inhibition of bacterial adherence to known receptors associated with bacterial colonization and establishment of infection.

Stashenko et al argues that the anti-LTA monoclonal antibodies directed against streptococcus mutans lipoteichoic acid(LTA) did not function to prevent adherence of the gram

positive pathogens, as the results associated with sucrose-dependent plaque accumulation assay pointed to the fact that LTA does not play a major role in adherence or plaque accumulation in vitro. The epitope to which the antibodies bound was a polyglycerol phosphate portion of the LTA molecule, wherein the antibodies to this epitope did not serve to define a therapeutic composition to provide plaque accumulation, a condition associated with gram positive bacterial infection and disease.

With respect to Applicant arguments directed to the importance of washing unbound anti-LTA antibodies away prior to evaluating the biological effects of the anti-LTA antibodies on adherence of bacteria to the assay surface, it is the position of the examiner that in vivo there would be no washing step in the claimed method of treating gram positive infection, and with increase anti-LTA concentration, the therapeutic effect of anti-LTA antibodies would be negated or minimized when a dosage for of an antibody composition of the binding specific disclosed by Stashenko et al, due to the bridging effect discussed by Applicant at page 12, paragraph 2, of the Amendment submitted July 14, 2003. Stashenko et al provides evidence that any anti-LTA antibody, administered at any dose, by any route of administration, to treat any type of gram positive bacterial infection would not result in treatment or prevention of gram positive bacterial infection in light of the antibodies serving to bring about a non-specific bridging effect rather than opsonization and elimination of the undesired gram positive bacteria.

24. With respect to Wergeland et al (1989, abstract), Applicant asserts that all of the samples were taken from patients with or suspected of having staphylococcal infections.

25. It is the position of the examiner that from the information provided by the abstract of the reference, both patients with current infection and blood donors WITHOUT current infection were evaluated. Wergeland et al was cited for showing that both infected and uninfected humans have antibodies to peptidoglycan, teichoic acid and lipoteichoic acid in their sera, and patient with current infection still have disease in the presence of anti-LTA antibodies. Not all

antibodies to lipoteichoic acid and the antigenic components thereof, are protective antibodies. All antibodies that specifically bind to lipoteichoic acid and fragments thereof, are not protective or preventive antibodies and would not serve to treat or prevent infection caused by gram positive bacterial pathogens. The scope of enablement rejection is maintained for reasons of record.

26. With respect to Yuji et al (1995, abstract, title), Applicant asserts that there are alternate explanations why Yuji's observation was made.

27. It is the position of the examiner that Yuji et al teach children with serum anti-lipoteichoic acid antibodies still evidence recurrent tonsillitis. The anti-lipoteichoic antibodies were not protective antibodies to prevent or treat infection. The key descriptors of the reference were directed to Streptococcus pyogenes and Staphylococcus aureus associated with tonsillitis and antibody titers to lipoteichoic acid. While it is true that tonsillitis can be caused by other pathogen other than Streptococcus pyogenes and Staphylococcus aureus, it is the position of the examiner that the Key Descriptors associated with the disclosure of Yuji et al are associated with the presence of anti-lipoteichoic acid antibodies in the serum of children with recurrent tonsillitis infection. Yuji et al was cited for showing that all anti-Lipoteichoic antibodies are not therapeutic antibodies that would serve to prevent infection; the infection of the patients were recurrent infections.

The cited references provide support for the scope of enablement rejection based upon the fact that while anti-LTA antibodies would serve to specifically bind to the epitope present in a gram positive bacteria, all of these antibodies would not serve to treat or prevent infection. The cited reference provide evidence that the epitope binding specificity of the antibody, the amount of antibody administered, the route of administration, all are critical elements to in a method of treating gram positive bacterial infection, especially in light of the fact that anti-LTA antibodies

do not predictably provide protection against infection but have been found in patients with autoimmune disease and in patients with recurrent gram positive bacterial infection.

28. With respect to antibodies that bind to the peptide of SEQ ID NO 1, an antibody would not necessarily be specific for a gram negative bacterium, Applicant asserts that the specificity of the anti-LTA antibodies of claims 32, 37 42 and 43 is not limited to binding only gram positive bacteria and if the anti-LTA antibodies bound to other potential pathogens, the antibodies of the instant method would provide for an increased benefit and could treat multiple infections simultaneously.

29. It is the position of the examiner that Applicants traversal is partially effective with respect to the binding specificity of the anti-LTA antibodies that bind to SEQ ID NO 1, Applicant did not address the fact that amino acids 3-7 share 100% sequence identity with a T-cell surface glycoprotein CD8 alpha chain precursor (Accession number P30433) which is not pathogen associated sequence, and binding of a T-cell surface glycoprotein by an anti-LTA antibody would not serve treat any type of bacterial infection but would result in binding a patient protein which could cause undesired negative side effects.

30. With respect to the recitation of SEQ ID No 2 to define the synthetic peptide of claims 36-37, antibodies that bind to this peptide would not by specific for gram negative bacterial infections, Applicant asserts that with increasing binding to other potential pathogens the patient would evidence increase benefit through the administration of the anti-LTA antibodies of the invention (see Amendment dated July 14, 2003, page 13 paragraph 4, and page 14, paragraph 1).

31. It is the position of the examiner that monoclonal antibodies that bind epitopes associated with cancer metastasis (JP10237099, 1998), an Fc domain fragment of the recited monoclonal antibody administered in the claimed method would also react with cancer, asthma, thrombosis and autoimmune disease associated epitopes which would not serve to provide an overall treatment method for gram positive bacterial infection. Antibodies that bind SEQ ID No 2

peptide or a fragment (Fc fragment) would lack disease specificity for gram positive bacteria and would the administered antibodies would evidence a dilution effect with respect to treatment of gram positive bacterial infection in patient which also have any one or more of parasite, cancer associated sugars chains, and autoimmune disease associated components.

32. With respect to peptides that are encoded by DNA that shares "at least 70% homology" with SEQ ID NO 88 or 89 as shown in Figure 12, Applicant states that "the antibody used in the invention does not need to bind LTA exclusively; it can also bind other antigens" and additionally questions "if this antibody only bound blood factor IX and did not bind LTA, then it would not fall under the scope of the invention.

33. It is the position of the examiner that the broad recitation of administration of any monoclonal chimeric light chains known in the art that share more than 70% amino acid sequence identity with SEQ ID No 89, or SEQ ID No 88 would not serve to treat gram negative bacterial infection, especially when the chimeric antibody shares 95.3% sequence identity over Applicant SEQ ID No 89, and only differs by 4 amino acids at the C-terminal of the chimeric antibody. The chimeric monoclonal of accession numbers AAW24532 evidences binding for blood Factor IX and would also be expected to bind to LTA based upon the overall high percentage of sequence identity (95.3%) and the chimeric monoclonal antibodies of the claims with more than 70% amino acid sequence identity are set forth as having LTA binding activity.

Additionally monoclonal antiidiotypic antibodies of accession numbers PL0082, and X58586 are known to evidence 94.3% sequence identity with SEQ Id NO 89, and 97.2 % sequence identity with SEQ Id No 88, respectively, and would be expected to bind to LTA as well as serve as an antiidiotypic antibody, which would not necessarily treat gram positive bacterial infection. The prior art supports the fact that antibody compositions, whether polyclonal or monoclonal, would unpredictably treat or prevent gram positive bacterial infection.

Only monoclonal antibody Mab 96-110 has been shown to predictably provide a

positive effect in vivo and would function in the claimed method, but not the full scope of the instantly claimed invention. While antibodies that are structural and functional homolog of Mab 96-110 could possibly be used in methods of purification and identification of a gram positive bacterial antigen in a sample, the application of the antibodies in vivo which bind to other patient proteins or function to induce immune responses to antigens that are not gram positive bacterial associated would not serve to treat or prevent infection. The scope of enablement rejection is maintained for reasons of record.

34. The rejection of claim 32 under 35 U.S.C. 102(b) as being anticipated by Dale et al (1994, abstract) is traversed on the grounds that:

a."[T]he Office has somehow read into this data that the binding of these antibodies to LTA is twice the level of background";

b.that "these antibodies have opsonic activity of 75% or greater"; and

c. "Dale does not provide any evidence showing that their antibodies possess these traits".

35. It is the position of the examiner that Dale et al discloses the claimed method that comprises the step of:

administering to a patient (mice) a pharmaceutical composition (anti-LTA antibody) that comprises an antibody to lipoteichoic acid of Gram positive bacteria (purified rabbit antibodies to LTA, see page 320, col. 1, paragraph 4) together with a pharmaceutically acceptable carrier (PBS:phosphate buffered saline; see page 320, col. 1, paragraph 4).

The recited functional limitations: "binds to lipoteichoic acid at a level twice background or greater", defines a titer for the antibody administered. The antibodies of Dale et al evidenced a titer of **128** (see page 320, col. 1, paragraph 4, four lines from the bottom of the paragraph). Clearly a titer of 128 is at a level twice background or greater.

With respect to opsonic activity (the definition of opsonic activity being understood to encompass (Stedman's Medical dictionary) the ability for binding to an antigen, as well as the

ability to enhance phagocytosis), it is the position of the examiner that the antibodies were purified antibodies that specifically bound to LTA on sensitized red blood cells (see page 320, col. 1, paragraph 4, hemagglutination), and also bound to type 24 streptococci gram positive bacteria (see page 320, col. 2, paragraph 2). Opsonic activity was demonstrated through blocking adherence of bacteria to epithelial cells, and providing significant protection against challenge in vivo (see Figure 1, page 320, col. 2, top of page). The antibodies specifically bound to and complexed with the gram positive bacteria, wherein the binding of the antibodies correlated with protection against death caused by gram positive infection.

Figure 1, shows that animals administered the antibody (anti-LTA) containing pharmaceutical composition had a 90% survival rate. 90% of the animals challenged were protected by the anti-LTA antibody containing pharmaceutical composition. The antibodies clearly provided protection against infection and facilitated clearance of the bacteria from the animal to protect against establishment of infection and death. The anti-LTA antibodies evidenced opsonic activity to provide complete protection against death in 18 of 20 animals (90% protection). The anti-LTA antibodies bound to the gram positive bacteria (opsonic activity of antibody) and prevented infection. The protective antibodies administered inherently have the recited opsonic activity in light of the fact that 90% of the animals were protected against established infection and death (see page 323, col. 1, paragraph 3, middle of paragraph "Once infection is established in mice, the organism tends to disseminate widely, leading to death from overwhelming sepsis"). Therefore the antibodies of Dale et al possess the recited functional characteristics of claim 32 and clearly anticipates the instantly claimed invention.

36. The rejection of claim 32 under 35 U.S.C. 102(b) as being anticipated by Fischer (WO93/19373) is traversed on the grounds that:

a. "[T]his reference does not provide any data indicating that the antibody preparations used contain an antibody that binds to LTA and that has the required binding and opsonic activities."; and

b. EP 783,520 B1 (also known as WO96/09321) showed the sera reacted "most strongly with a protein antigen".

37. It is the position of the Examiner that WO93' disclose antibodies/immunoglobulin that are immunoreactive with lipids, polysaccharides and proteins (see page 17, first paragraph, lines 5-8); the invention of Fischer WO93' includes antibodies immunoreactive with lipoteichoic acids that comprise both a lipid component and a saccharide component.

A method of preparing antigen disclosed in WO93' comprises TCA extraction followed by ethanol precipitation (see WO93', page 31, Example 1, bottom paragraph 3); this combination of methods steps isolates bacterial teichoic acid containing antigen (see Naumova et al, 1980, reference cited in Applicants US-PTO 1449, dated October 7, 2002, page 6 of 9) and is the method of preparing antigen used to immunize a host to produce immunoglobulin antibodies (see page 38, Example 6, Figures 5 and page 17, paragraph 1, second half of paragraph; page 18, paragraphs 1-2 and page 19, paragraph 1). Immunoglobulin compositions produced through immunization with teichoic acid containing antigen, would induce and produce an antibody specific for a gram positive bacteria (Staphylococcus epidermidis) lipoteichoic acid. The antibodies of WO93' are disclosed to be specific for lipids, polysaccharides, proteins and bacterial cell components (last sentence page 18, WO93').

The disclosed compositions of antibodies are administered in a method of treating gram positive bacterial infection (see claims 27, 28 and all figures).

38. In response to Applicant's assertion that the antibody reacted most strongly with a protein antigen, it is the position of the examiner that antibodies to proteins are not excluded from the compositions administered in the claimed methods, and the antibodies of Fischer WO93' are disclosed to immunoreact with lipids and saccharide molecules (see WO96/09321 or EP783520,

reference cited by Applicant, Example 15, paragraph 3, and Figures 2 and 5), produced by a method of immunization with TCA/ethanol treated gram positive bacteria, wherein this method is known in the art (see Naumova et al, 1980, reference cited in Applicants US-PTO 1449, dated October 7, 2002, page 6 of 9) to result in an immunogen/antigen containing composition of lipoteichoic acid molecules (molecules known to comprise saccharides, amino acids and either ribitol or glycerol phosphate).

The immunoglobulin antibodies of WO93' are immunoreactive with the antigen obtained from the Hay strain (see claims 11-14). The antigen obtained by TCA extraction (see claim 14). The extracted antigen comprising lipoteichoic antigens, wherein the immunoglobulin was disclosed and claimed in a method of treating staphylococcal infection (a gram positive bacteria), through administering the immunoglobulin in a pharmaceutical composition. While the term anti-LTA antibodies is not used n the WO93' document, a gram positive bacterial source of the antigen (strain Hay, Staphylococcus epidermidis), and a well known method of isolating bacterial teichoic acid antigen, were both used in obtaining antibodies for treating human gram positive bacterial infection. The antibodies inherently comprising at least one anti-LTA antibody.

No evidence has been made of record showing that the method of WO93' would not result in the instantly claimed invention. By all comparable data, the method of treating gram positive bacterial infection of WO93' inherently anticipates the instantly claimed invention (see claim 28, WO93'). The presence of anti-protein antibodies in the composition of WO93' are not excluded by the instant invention and therefore, arguments directed to anti-protein antibodies are not commensurate in scope with the instantly claimed invention.

39. The rejection of claims 32-33 under 35 U.S.C. 102(e) as being anticipated by Fattom et al (US Pat. 5,770,208) is traversed on the grounds that:

a. "The "336" antigen," which is not identified as LTA"; and

b.describes the antigen in general terms;

c.the opsonic activity displayed in Figure 2 was a measurement of antibodies developed to a conjugate vaccine of the 336 antigen and exotoxin A; and concludes that the method is not taught to be a method which administers a pharmaceutical composition comprising an antibody that binds to LTA which has the requisite binding and opsonic activity.

40. It is the position of the examiner that Fattom et al claims a method that comprises the step of administering isolated antibodies to a subject, wherein the antibodies are directed to a B-linked hexosamine antigen, and two polysaccharide antigens of a gram positive bacteria, wherein B-linked hexosamine antigens are known to be teichoic acid associated antigens for gram positive bacteria (Karakawa et al (Jan. 1975, abstract) teach a teichoic acid that comprises fucosamine, a species of hexosamine); Archibald et al (1973, abstract title and descriptors) teach Staphylococcus lactis to comprise hexosamines in the cell wall; Wu et al (1971, abstract, title and descriptors) teach Staphylococcus aureus to comprise hexosamines associated with teichoic acid).

While Fattom et al does not describe the "336" antigen as a teichoic acid associated antigen, the antibodies would specifically bind to β-hexosamine carbohydrate components associated with gram positive bacterial teichoic acid antigens.

Fattom et al describes the "336" antigen in general terms, the antibodies administered to a subject for immunotherapy were specifically described to bind to β-hexosamine of a gram positive bacterium, and were disclosed as providing protection against infection.

The instantly claimed methods administer antibodies directed to any portion of any lipoteichoic acid molecule which include sugars, carbohydrates associated with the teichoic acid, and polyols of ribitol phosphate or glycerol phosphate (definition provided by Stedman's medical dictionary). The anti-LTA antibodies of the instant claim 32 may specifically bind any antigen portion of LTA, that portion not specifically defined by a specific chemical structure from any species or strain of gram positive bacteria.

As hexosamines are molecules known to be associated with teichoic acids of gram positive bacteria (see abstracts cited above), and the immunotherapic antibodies of Fattom et al specifically bound hexosamine, inherently the antibodies of Fattom et al evidence the recited functional characteristics of the antibodies administered in the instantly claimed methods.

The asserted requisite binding and opsonic activity of the antibodies used in the instantly claimed methods, are disclosed and claimed by Fattom et al who administered antibodies defined by a species of hexosamine antigen which antibodies served to provide effective immunotherapy (see claims 1-23 of Fattom et al) through enhancing opsonic activity.

The anti-LTA antibodies of instant claims 32-33 have not been distinguished from the antibodies of Fattom et al. Fattom et al still anticipates the instantly claimed invention.

41. The rejection of claim 32 under 35 U.S.C. 102(b) as being anticipated by Ichiman et al (1989) is traversed on the grounds that:

a."the Office again speculates that Ichiman generated anti-LTA antibodies";

b. "The biochemical properties of the protective antigens of unencapsulated strains have not been elucidated";

c.Ichiman provides no opsonic activity data for the prepared sera; and

d.does not provide all the elements of the claimed invention.

42. It is the position of the examiner that unencapsulated isolates of Staphylococcus epidermidis are covered by teichoic acid (see WO93/09811, Fattom et al provides evidence that unencapsulated strains of S.epidermidis are covered in teichoic acid immunogen. See Fattom et al, page 8, lines 9-11) and that the strains of Ichiman et al were unencapsulated isolates of Staphylococcus epidermidis.

The unencapsulated isolates of Staphylococcus epidermidis inherently comprised teichoic acids based upon the fact that unencapsulated isolates of Staphylococcus epidermidis produce teichoic acid which are surface associated. The examiner did not speculate with respect

to the presence or absence of teichoic acid antigens on the surface of the S.epidermidis strains of Ichiman et al as S.epidermidis was known at the time of filing of the instant specification to produce teichoic acids on the surface of unencapsulated strains.

With respect to the biochemical properties of the protective antigens of the unencapsulated strains not having been elucidated, it is the position of the examiner that the biochemical structure of the LTA of the claims is broadly claimed, and no specific chemical structure is required for the LTA molecule of independent claim 32. Any protective antibody that will specifically bind and opsonize a gram positive bacteria is claimed for use in the instant methods as long as the administered composition comprises anti-LTA antibodies.

While Ichiman et al does not provide insight into the chemical structure of the surface immunogen, the reference does provides insight into at least one biochemical property of the administered immunogen, specifically the immunogen is heat stable (see title of Ichiman et al). The heat stable immunogen of Ichiman et al induced protective antibodies. Teichoic acids are polysaccharide associated immunogens and polysaccharide immunogens are heat stable antigens.

While Ichiman et al does not carry out an opsonization assay in vitro, the reference shows the antibodies provided enhanced protective opsonic activity relative to background, in light of the data shown in Table 4 (page 283, top), wherein the antibodies administered showed 100% protection at a dilution factor of 1:3 relative to control animals that did not receive the protective antibody.

Therefore the binding of the pharmaceutical composition that comprised antibodies directed against surface associated antigens of S.epidermidis that comprise teichoic acid antigens bound to the antigens at least twice background (titer effective for protection was 1:3 while the control showed no protection at Zero dilution) and the antibodies enhanced opsonization by 100% to evidence protection of all animals in the group when all control animals died due to the absence of the administered protective antibody.

The examiner made no assumptions, but applied Ichiman et al against claim 32, based upon the what was known about the presence of teichoic acids being present on the surface of S.epidermidis unencapsulated strains, at the time of filing of the instantly claimed invention.

While Ichiman et al did not know the biochemical structures present in the surface of unencapsulated S.epidermidis in 1989, by 1993, unencapsulated strains were found be covered by teichoic acid (Fattom et al WO93', page 8, lines 9-11). The antibodies of Ichiman et al were generated by the same or equivalent method of Applicant and administered to same or equivalent patient for providing a therapeutic or prophylactic effect. Ichiman et al carried out the claimed method of administering a pharmaceutical composition of antibodies to a patient, wherein the antibodies provided treatment, a prophylactic effect against S.epidermidis infection. The antibody containing pharmaceutical composition of Ichiman et al, inherently comprising anti-LTA antibodies (see Ichiman et al Table 4), because the surface exposed antigens of unencapsulated Staphylococcus epidermidis comprise teichoic acid immunogens.

Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

Conclusion

43. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

44. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
45. Fischer et al (US Pat. 6,610,293) is cited to show compositions of chimeric immunoglobulin chain antibodies that bind to lipoteichoic acid of gram positive bacteria.
46. Ginsburg et al (1988) is cited to show Lipoteichoic acid/anti-lipoteichic acid complexes induce superoxide generation by human neutrophils.
47. Mancuso, G et al (1994) is cited to show anti-lipoteichoic acid antibodies enhance release of cytokines by monocytes sensitized with lipoteichoic acid and raises the question as to whether naturally occurring anti-LTA antibodies contribute to release of cytokines associated with gram positive septic shock (see page 1472, col. 1, paragraph 3, last sentence).

48.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
September 22, 2003

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